REMARKS

Reconsideration and withdrawal of the rejections of the claimed invention is respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1-3, 5, 6, 12-29 are pending in this application. Claim 1 has been amended to include the element of previous claim 8. Claims 2, 3 and 5 have been amended to better clarify the relationship of the formulation and the patch. Although new claims 28 and 29 are directed to a non-elected invention, both claims are dependent upon the subject matter of claim 1 and should be rejoined upon allowance of claim 1. *See MPEP 821.04.*

The amendment to the specification on page 16 was made to correct an inadvertent error with regard to the unit of measurement for the flux (i.e. ---µg/(cm^2*h)--- instead of "g/(cm^2*h)")

No new matter has been added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Second Request for removal of 3rd party document from Image File Wrapper

Upon review of the Image File Wrapper (IFW) for this application, in addition to the papers associated with the Office Action which were entered into the IFW on 7 February 2008, there was also a file described as "Claims" which was also entered on this date.

The applicants did not submit this file and the claims in this document appear to be directed to another application (SN: 11/680,727 – "X-Ray Recording Device with an X-Ray Detector and an X-Ray Emitter") which is not owned by the applicants or is being proseeuted by the applicants' representatives. There was no indication in the Office Action that this was intended to be part of the papers to be mailed to the applicants.

As this paper appears to be unrelated to the present invention and was inadvertently cntered by the PTO, the applicants request removal of this file from the IFW for this application.

II. THE 35 U.S.C. 103(a) REJECTION HAS BEEN OVERCOME

Note: As there has been no indication that the restriction/election of species has been withdrawn or that the scope of the examination was expanded beyond the applicants' elected species, the invention was presumed to be examined for the election whercin:

1. The patch is a matrix-type patch
2. The adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer
3. The another penetration enhancer is an N-methyl pyrrolidone
4. The preservative is an organic acid
5. The backing comprises of polyester.

As such, by virtue of the restriction/election of species requirement, this election was deemed to be patentably distinct from other elections which could have been made by the applicants.

Claims 1-6, 8 and 11-25 were rejected as allegedly being obvious by Fischer et al. (U.S. Patent 6455066 – "Fischer") as applied to claims 1-6 and 11-22 above and further in view of Nielsen (U.S. Patent 6171594). As claim element of previous claim 8 is now an element of claim 1 as amended above, the applicants' response above also address the rejection of claim 8 from the previous Office Action.

The applicants request reconsideration of this rejection for the following reasons.

In order to establish *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art reference or be within the knowledge of those of ordinary skill in the art. *See MPEP 2143.03.* In addition, for the purposes of this application, any reference which fails to teach any of the elected elements described above, would be considered to be a patentably distinct invention. *See MPEP 806.04(h).* However, Fischer fails to teach or suggest all of the limitations of the applicants' transdermal formulations.

First, the applicants' invention is directed toward a ***transdermal*** formulation whereas the invention of Fischer is directed toward an ***intradermal*** composition. The differences in administration is well known in the art and is even addressed by Fischer themselves in the

background of their invention (see col. 1, lines 39-48).[1] As one of ordinary skill in the art would recognize that intradermal administration is intended to ***avoid*** any transdermal absorption, the Fischer reference would not be readable upon or suggestive of the applicants' transdermal formulation.

Second, Fischer is directed toward the delivery of an ***anesthetic*** whereas the applicants' transdermal formulation is directed toward delivery of an ***opioid analgesic*** from the phenanthrene group which is consistent with their disclosed methods of delivery, i.e. Fischer wants localized delivery of their anesthetic and to avoid systemic delivery whereas the applicants' invention wants to provide systemic delivery to maximize the pain relief associated with the opioid analgesic.

Moreover, Fischer recognized that the behavior of a penetration enhancer is strongly dependent on the drug (see col. 2, lines 35-41) and as such one of ordinary skill in the art would not impute the penetration activity of aloe vera with an anesthetic as being predictive of the activity with an opioid analgesic and in this instance, it is uncertain what relevance of such predictability would be as Fischer and the applicant are directed toward inventions with opposite modes of action.

Third, Fischer also lacks a teaching for some of the elected features of the applicants' claimed invention, i.e. Fischer does not teach a matrix-type patch or that the adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer.

The applicants further add that Fischer is silent as to the adhesive being comprised of styrene-butadiene-styrene block copolymer. However, while Nielsen refers to an adhesive matrix of styrene-butadiene-styrene copolymer, there is no reason offered from either Fischer or Nielsen for making this combination.

Nielsen is not directed toward intradermal use as in Fischer and even if it had been directed to transdermal use, Fischer's invention actively teaches away from transdermal use. Nielsen uses their adhesive not for dermal administration of an analgesic, but for securing and

---

[1] "In general, drug administration via the skin is divided into two categories: 1) ***transdermal*** administration and 2) ***intradermal*** administration. Transdermal administration involves transport through the skin and into the blood stream to treat systemic diseases. One the other hand, intradermal administration is intended to impart a cutaneous effect, while keeping the pharmocological effects of the drug localized to the intracutaneous regions of drug penetration and deposition. ***Ideally, intradermal absorption occurs with little or no systemic absorption or accumulation.***" (emphasis added)

sealing an ostomy (an operation where an artificial opening is formed) appliance which is unrelated to Fischer or the applicants' invention.

Moreover, there was no reason offered in the respective teachings of Fischer or Nielsen or from the generally available knowledge of those of skill in the art as to why that particular feature of Fischer needed to be modified, i.e. while it can be obvious to try and modify an invention if there are a finite number of solutions, there was no reason for one of ordinary skill in the art, lacking the applicants' claims as a blueprint, to select the use of a specific adhesive, as the necessary element to be modified; one of ordinary skill in the art could have tried any number of Fischer's other elements of their invention for modification (e.g. different active agent, different reservoirs system, etc.) such that rather than a finite number of solutions, there was an infinite number of solution for an as undetermined problem.

Therefore, for any of the above reasons, claim 1 and the claims dependent thereon are not obvious over the combination of Fischer and Nielsen.

Response to arguments presented in the final rejection

1. Interpretation of intradermal vs. transdermal administration was factually incorrect in the final rejection

The arguments presented in the final rejection appeared to concede that there are differences between intradermal and transdermal delivery.[2] The final rejection stated that:

> "The Applicant's claim uses the same delivery system; therefore, for the drugs to be delivery (sic) from the skin to the inside of the skin, then ***the drugs would have to be transdermally delivered, then intradermally delivered.***" (page 4, lines 3-5 of the final rejection (emphasis added))

However, this analysis is incorrect and appears to confuse the definition of intradermal and transdermal administration.

Intradermal administration is the transportation of a drug into the skin, more specifically, into the dermis, **without the uptake into the venules and arterioles**, which only

---

[2] The applicants attach to this response further evidence of the differences between intradermal and transdermal delivery from Allen et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (8th Edition)*, pages 298 and 448, (2005). – "Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances ***through the skin*** and ***into the general circulation for their systemic effects.*** pg. 298 (emphasis added). "A number of substances may be effectively injected into the corium [the dermis], the more vascular layer of the skin just beneath the epidermis. These substances include various agents for diagnostic determinations, ***desensitization***, or immunization." pg. 448 (emphasis added).

populate the deeper layers of the skin, i.e. the hypodermis. See page 145 from *Concepts of Human Anatomy and Physiology*, Wm. C. Brown Publishers, (1992) which is attached to this response which includes a diagram of the integumentary system (skin).

In other words, the drug penetrates from the vehicle (e.g. in a patch) through the *Stratum corneum* into the epidermis and possibly into the dermis, however without reaching the capillaries and the blood stream in a pharmacologically relevant amount. Intradermal administration thus serves for the topical administration of a drug which should be effective in the skin. An example for these drugs are anesthetics. Intradermal administration is intended to impart a cutaneous effect. Intradermal absorption occurs with little or no systemic absorption.

In contrast, **transdermal administration** includes necessarily all of the above described aspects of intradermal administration. However, in the case of transdermal administration, the further transportation of the drug in the vicinity of the capillaries and the uptake of the drug by the blood capillaries are desired, i.e. into the hypodermis. An example for these drugs are analgesics. Transdermal administration is intended to impart a systemic effect. Transdermal absorption occurs predominantely with systemic absorption into the arterioles and venules, after the absorption into the skin has occurred.

Therefore, the Examiner's statement is factually incorrect as intradermal administration does NOT occur after transdermal delivery. Intradermal administration speaks to an administration method which is different and distinct from transdermal administration and is even recognized as such within the Fischer reference (see again col. 1, lines 39-48).

2. Use of same ingredients (aloe composition) in Fischer was not only for a different means of administration, but also for a different class of compounds

Fischer discloses a patch for the intradermal administration (not transdermal) of local anesthetics (col. 1, lines 7-10). These anesthetics may be selected from lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, procaine, chloroprocaine, ropivacaine, dibucaine, etidocaine and benzocaine (2/42-45). Anesthetics need to be administered locally to the skin, and thus intradermal administration is desired and is recognized as such in the definition for intradermal administration provided in Allen. Fischer also mentions analgesics, however, only in so far as they have the effect of "local anesthetics". Therefore, also these drugs are intended for a topical and intradermal administration.

Some anesthetics (amide and ester type anesthetics) are systemically toxic. Therefore, an exclusively intradermal absorption is not only desired in view of the local topical effect of the

drug, but also due to the fact that transdermal transportation and systemic absorption of anesthetics need to be avoided.

Fischer states that the majority of dermal drug formulations and penetration agents are for transdermal administration. Therefore, a need exists for penetration agents for intradermal local administration, e.g. of anesthetics.

Fischer teaches that aloe compositions represent such intradermal penetration agents, which enhance the penetration of topically applied local anesthetics through the *Stratum corneum* into the epidermis or dermis, in the absence of systemic absorption of the anesthetic (= transdermal administration).

Specific formulations disclosed by Fischer include those formulations which comprise an adhesive, the adhesive having the functions of releasing the anesthetic and adhering the anesthetic matrix to the skin (col. 8, lines 38-41), e.g. patches. Fischer mentions a large variety of adhesives. It is first stated that three basic types commonly used are polyisobutylenes, silicones, and acrylics. Preferred adhesives are compositions based on natural rubber, synthetic rubber, polyacrylates, polyvinylacetate, polydimethylsiloxane, hydrogels (of polyvinylpyrrolidone). It should be noted that this enumeration of adhesives practically includes all adhesives which are normally used in dermal patch-type formulations and thus does not represent a specific technical teaching in connection with intradermal/transdermal formulations and adhesives used therein.

However, in the following of the Fischer document, the usable adhesives are concretized by specifically referring to polyacrylates. Fischer enumerates some of them, namely polybutylacrylate, polymethylacrylate, poly-2-ethylhexyl acrylate. In Examples 1 and 2 the patch comprises an acrylate matrix. Finally in claim 1 a patch is claimed which eomprises an acrylic adhesive, lidocaine as anesthetic and soybean oil as penetration agent. According to claim 2, an aloe composition may be added as further penetration agent.

It may thus be summarized that Fischer discloses dermal formulations which are more specifically intradermal formulations and no transdermal formulations, which comprise an anesthetic, the patch for intradermal administration being fabricated with an acrylic polymer as the adhesive.

3. Use of the aloe composition

As presented above, the transdermal administration of a drug comprises the intradermal transportation of the drug through the *Stratum corneum* into the epidermis or dermis and the

further (transdermal) transportation of the drug through the deeper layers of the skin to the blood capillaries where the drug is systemically absorbed into the blood stream.

According to Fischer et al. aloe compositions represent intradermal penetration agents which enhance the penetration of topically applied local anesthetics through the *Stratum corneum* and into the epidermis or dermis, and it is expressly stated, that this intradermal absorption occurs in the absence of systemic/transdermal absorption of the anesthetic.

In view of this teaching of Fischer et al. one of ordinary skill would not have used an aloe composition in a formulation comprising an analgesic with the expectation of obtaining a transdermal formulation which delivers the analgesic from the formulation into the blood stream.

The description of the present patent application gives evidence that aloe compositions in fact and different from the Fischer document have the function of transdermal penetration agents, cf. Examplc 1. According to Table 1 batch 002 comprises 5 % buprenorphine and 20 % *Aloe vera*, whereas batch 003 comprises 10 % buprenorphine and 10 % *Aloe vera*. The flux of buphrenorphine comprised in these compositions through hairless mouse skin is measured. Despite the very different amount of buprenorphine (the amount is doubled from batch 002 to batch 003, 5 % → 10 %), the buphrenorphine flux is almost identical (0.8 μg/(cm^2*h) → 0.9 μg/(cm^2*h)), this result being due to the doubled amount of *Aloe vera* in batch 002 as compared with batch 003, and the penetration enhancing function of *Aloe vera*.

4. Nielsen reference does not lead one of ordinary skill in the art to modify the Fischer reference in the manner prescribed in the final rejection

The Nielsen invention relates to adhesive agents for application to human or animal skin. More spccifically, when considering the Nielsen invention reference as a whole, it is clear that it is directed to the use of the adhesive agent for securing of ostomy appliances and sealing around an ostomy, for wound dressings, for securing of devices for collecting urine, wound drainage bandages, orthoses and prostheses and for protection of skin areas and parts of the body against pressure, impacts, friction and/or exudates from the body.

The Nielsen invention is totally silent as regards the intradermal or transdermal administration of drugs. Furthermore, the Nielsen invention is totally silent as regards the use of analgesics. Thus, one of ordinary skill would not have taken this document into consideration when trying to find a solution for the problem which is solved by the present invention, namely the development of formulations for the transdermal administration of an analgesic.

But even if the skilled person had taken the Nielsen invention into consideration, he would not have found any hint about the favorable properties of aloe compositions for transdermal administration of drugs, especially analgesics, and he would not have found any hint about the favourable combination of an analgesic and an aloe composition with a specific synthetic rubber adhesive, namely a styrene-butdiene-styrene polymer, which results in a formulation which shows a high flux of the analgesic through the skin and for which this high flux is preserved over a long time due to the absence of any crystallisation of the drug in the matrix.

In fact, as regards the aloe composition, the Nielsen invention only mentions typical and known properties of aloe, e.g. its antibacterial effect and its advantageous properties for wound healing. Furthermore the Nielsen invention only mentions the use of styrene-butadiene-styrene copolymers as adhesives for e.g. ostomy or incontinence appliances, the adhesive comprising the aloe composition to improve wound heeling. According to Nielsen it is advantageous to incorporate the aloe composition in the adhesive to achieve a better protection of the skin against the aggressive action of excretions from the body.

Thus, when starting from the Fischer invention and reading the Nielsen invention, one of ordinary skill would not have obtained any usable information that it might be advantageous or even just possible, when starting from the intradermal formulations of Fischer for the topical administration of an anesthetic into the skin,

- to replace the anesthetic by an analgesic and
- to replace the acrylate adhesive by a styrene-butadiene-styrene copolymer adhesive

in order to obtain a transdermal formulation for the systemic administration of an analgesic through the skin into the blood stream.

5. Evidence of secondary considerations

When considering the applicants invention as a whole, the present invention provides a solution for the problem of imparting a pharmaceutical formulation with properties which enable an opiod analgesic to be transdermally administered. The solution for this problem consists in

- a transdermal formulation comprising
- a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer,

- an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient and
- an aloe composition as transdermal penetration agent.

With respect to amended claim 1, the formulation comprises a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer.

The inventors have carried out comparative experiments which are similar to Example 1 in the specification and which are now presented for the first time with this submission in the Declaration by Dr. Elisabeth Meyer.

In Example 1 of the description of the present application experiments with different matrix patches are presented. The results are summarized in Table I on page 16 of the description. A matrix patch is provided which comprises a mixture of buprenorphine (the analgesic), an aloe (the transdermal penetration agent) and a styrene-butadiene-styrene polymer (the adhesive). Flux experiments with hairless mouse skin reveal buprenorphine fluxes in the range from 0.8 to 2.3 $\mu g/cm^2*h$ and the transdermal penetration effect of aloe compositions.

In the comparative experiments the styrene-butadiene-styrene polymer (the adhesive) was replaced by several acrylate adhesives, i.e. the adhesive which is disclosed by Fischer as the usual adhesive in combination with the intradermal penetration agent (the aloe composition) and the drug.

The results as disclosed in the description and the results of the comparative experiments are presented in the following table below (see next page):

Adhesive type	PSA	Buprenorphine (% w/w)	*Aloe vera* (% w/w)	Flux (hairless mouse skin)	**Formation of crystals**
Examples of the Present Invention (cf. Table I of the invention, page 16)					
Styrene-butadiene-styrene polymer	DT 6173	15	20	2.3 µg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	5	20	0.8 µg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	10	10	0.9 µg/(cm^2*h)	–
Comparative Examples					
Acrylate-vinylacetate with carboxy groups	DT 2825	10	10	1.1 µg/(cm^2*h)	+
Acrylate-vinylacetate with hydroxyl groups	DT 2287	10	10	1.1 µg/(cm^2*h)	+
Acrylate with functional hydroxy groups	DT 2510	10	10	1.3 µg/(cm^2*h)	+
Acrylate-vinylacetate without functional groups	DT 4098	10	10	1.5 µg/(cm^2*h)	+

It should first be noted that in the description of the present application the fluxes are accidentally given as g/(cm^2*h). In fact, also in the case of the invention the fluxes are in the micro gram range and should read as µg/(cm^2*h) which is corrected in the specification.

When comparing the results of the above experiments in which the patches comprise 10 % (w/w) *Aloe vera* it turns out that the fluxes which are obtained with the styrene-butadiene-styrene polymers as adhesive (according to the invention) and with the acrylates as adhesives (comparative examples) are similar. ***However, with the acrylate polymers a disadvantageous crystallization of the drug (buprenorphine) in the matrix is observed over the time.*** Such a crystallization reduces the long term stability of the formulations and the amount of drug available for the transdermal penetration is very disadvantageous for transdermal applications, for which a relatively high concentration of the dissolved drug in the pharmaceutical formulation is needed. This disadvantageous crystallization effect can be avoided using the styrene-butadiene-styrene polymers of the invention.

The Fischer invention does not comprise any hint that, different from acrylates, styrene-butadiene-styrene polymer adhesives in pharmaceutical formulations can prevent crystallization of the drug, whereby the long term stability of formulations comprising buprenorphine and an aloe composition are improved and whereby the formulations may be used as transdermal formulations.

6. Conclusion

Therefore, the combination of Fischer and Nielsen does not render the applicants' claimed formulation to be obvious as there is never any teaching or direction that an aloe composition is suitable for use with an opioid analgesic from the phenanthrene group for providing transdermal administration; there is no teaching or direction which would lead one of ordinary skill in the art to select an element from Nielsen into Fischer and provide a reasonable expectation of success for the proposed modification and because there is no hint of the unexpected results achieved by the applicants for their claimed formulation from Nielsen and Fischer.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems

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Designer: Doug Smock
Compositor: Peirce Graphic Services, LLC.
Printer: Courier—Kendallville

351 West Camden Street
Baltimore, MD 21201

530 Walnut Street
Philadelphia, PA 19106

Printed in the United States of America

Library of Congress Cataloging-in-Publication Data

Allen, Loyd V.
Ansel's pharmaceutical dosage forms and drug delivery systems / Loyd V. Allen Jr., Nicholas G. Popovich, Howard C. Ansel.—8th ed.
p. ; cm.
Rev. Ed. of: Pharmaceutical dosage forms and drug delivery systems / Howard C. Ansel, Loyd V. Allen, Jr., Nicholas G. Popovich. 7th ed. c1999.
Includes bibliographical references and index.
ISBN 0-7817-4612-4
1. Drugs—Dosage forms. 2. Drug delivery systems. I. Title: Pharmaceutical dosage forms and drug delivery systems. II. Popovich, Nicholas G. III. Ansel, Howard C., 1933– IV. Ansel, Howard C., 1933– Pharmaceutical dosage forms and drug delivery systems. V. Title.
[DNLM: 1. Dosage Forms. 2. Drug Delivery Systems. QV 785 A427a2004]
RS200.A57 2004
615'.1—dc22 2004048276

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Transdermal Drug Delivery Systems

11

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Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. In 1965 Stoughton first conceived of the *percutaneous absorption* of drug substances (1). The first transdermal system, Transderm Scop (Ciba, now Novartis) was approved by the Food and Drug Administration (FDA) in 1979 for prevention of nausea and vomiting associated with travel, particularly by sea.

Evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and/or its metabolites in the urine, and clinical response of the patient to the therapy. With transdermal drug delivery, the blood concentration needed to achieve therapeutic efficacy may be determined by comparative analysis of the patient's response to drug blood levels. For transdermal drug delivery, it is considered ideal for the drug to migrate through the skin to the underlying blood supply without buildup in the dermal layers (2). This is in direct contrast to the types of topical dosage forms discussed in the previous chapter, in which drug residence in the skin, the target organ, is desired.

As discussed in the previous chapter, the skin is composed of the stratum corneum (the outer layer), the living epidermis, and the dermis, which together provide the skin's barrier layers to penetration by external agents (see Fig. 10.6). The film that covers the stratum corneum is composed of sebum and sweat, but because of its varied composition and lack of continuity, it is not a significant factor in drug penetration, nor are the hair follicles and sweat and sebaceous gland ducts, which constitute only a minor proportion of the skin's surface.

Percutaneous absorption of a drug generally results from direct penetration of the drug through the stratum corneum, a 10- to 15-μm-thick layer of flat, partially desiccated nonliving tissue (3, 4). The stratum corneum is com-

than in the gluteal area. If a series of injections are to be given, the injection site is usually varied. To be certain that a blood vessel has not been entered, the clinician may aspirate slightly on the syringe following insertion of the needle to observe any blood entering the syringe. The volume of medication that may be conveniently administered by the intramuscular route is limited, generally to a maximum of 5 mL in the gluteal region and 2 mL in the deltoid of the arm.

The Z-track technique is useful for intramuscular injections of medications that stain upper tissue, such as iron dextran injection, and those that irritate tissue, such as diazepam, by sealing these medications in the lower muscle. Because of its staining qualities, iron dextran must be injected only into the muscle mass of the upper outer quadrant of the buttock. The skin is displaced laterally prior to injection, then the needle is inserted and syringe aspirated, and the injection performed slowly and smoothly. The needle is then withdrawn and the skin released. This creates a Z pattern that blocks infiltration of medication into the subcutaneous tissue. The injection is 2 to 3 inches deep, and a 20- to 22-gauge needle is used. To reduce further any staining of upper tissue, usually one needle is used to withdraw the iron dextran from its ampul and replaced with another for the injection.

Subcutaneous Route

The subcutaneous route may be used for injection of small amounts of medication. Injection of a drug beneath the skin is usually made in the loose interstitial tissue of the outer upper arm, the anterior thigh, or the lower abdomen. The site of injection is usually rotated when injections are frequently given, as with daily insulin injections. Prior to injection, the skin at the injection site should be thoroughly cleansed. The maximum amount of medication that can be comfortably injected subcutaneously is about 1.3 mL, and amounts greater than 2 mL will most likely cause painful pressure. Syringes with up to 3-mL capacities and 24- to 26-gauge needles are used. These needles have cannula lengths of three-eighths of an inch to an inch. Most typically, subcutaneous insulin needles are 25 to 30 gauge with length of five-sixteenths to five-eighths of an inch. Upon insertion, if blood appears in the syringe, a new site should be selected.

Irritating drugs and those in thick suspension may produce induration, sloughing, or abscess and may be painful. Such preparations are not suitable for subcutaneous injection.

Intradermal Route

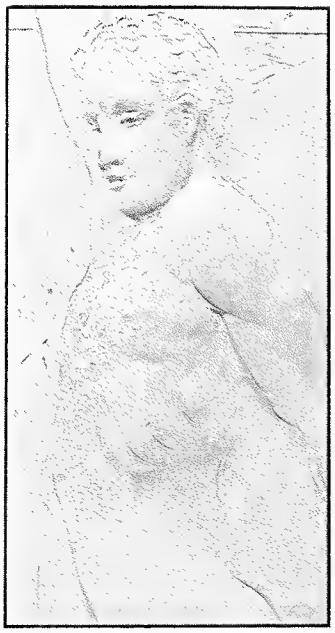
A number of substances may be effectively injected into the corium, the more vascular layer of the skin just beneath the epidermis. These substances include various agents for diagnostic determinations, desensitization, or immunization. The usual site for intradermal injection is the anterior forearm. A short (three-eighths of an inch) and narrow (23- to 26-gauge) needle is usually employed. The needle is inserted horizontally into the skin with the bevel facing up. The injection is made with the bevel just disappearing into the corium. Usually only about 0.1 mL may be administered in this manner.

Specialized Access

When it is necessary to administer repeated injections over time, it is prudent to employ devices that provide continued access and reduce pain associated with administration.

Several types of central venous catheters are used in institutions and on an outpatient basis for a variety of parenteral medications (e.g., cancer chemotherapy, long-term antibiotic therapy, total parenteral nutrition solutions). They can remain in place for a few days to several months. When not in use, they require heparinization to maintain patency of the catheter lumen.

The use of indwelling plastic catheters reduces the need for multiple punctures during intravenous therapy. Composed of polyvinyl chloride, Teflon, and polyethylene, these should be radiopaque to ensure that they are visible on radiographs. Usually, these must be removed within 48 hours after insertion. The choice of catheter depends on several factors, including



Third Edition

Concepts of Human Anatomy and Physiology

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Unit and chapter opening illustrations—Yvette Mintzberg—Montreal, Canada

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Library of Congress Catalog Card Number: 91-70853

ISBN 0-697-09716-1

Printed in the United States of America by Wm. C. Brown Publishers, 2460 Kerper Boulevard, Dubuque, IA 52001

10 9 8 7 6 5 4 3 2 1

CLINICAL INVESTIGATION

27-year-old male is involved in a gasoline explosion, sustaining burns to the face, neck, chest, and arms. Upon arrival at the emergency room, he complains of intense pain in the face and neck, which exhibit extensive blistering and erythema (redness). These findings are all curiously absent on the burned chest and arms, which have a pale, waxy appearance.

Examination reveals the skin on the patient's chest and arms to be leathery in texture and without sensation, including pain. The emergency room (E.R.) physician comments to an observing medical student that third degree burns are present on the skin of these regions and that excision of the burn eschar (traumatized tissue) with subsequent skin grafting will be required.

Why is the area of second degree burn red, blistered, and painful, while the third degree burn is pale and insensate (without sensations, including pain)? Why will the chest and arms require skin grafting while the face and neck probably will not?

Hints: Think in terms of functions of the skin, and survival of the germinal cells in functioning skin. Examine carefully figures 7.1 and 7.13. ■

The Integument as an Organ

The integument (skin) is the largest organ of the body, and together with its epidermal structures (hair, glands, and nails), it constitutes the integumentary system. It has adaptive modifications in certain body areas that accommodate protective or metabolic functions. The integument is a dynamic interface between the continually changing external environment and the body's internal environment and aids in maintaining homeostasis.

Objective 1. Explain why the integument is considered an organ and a component of the integumentary system.

Objective 2. Describe some common clinical conditions of the integument that result from nutritional deficiencies or body dysfunctions.

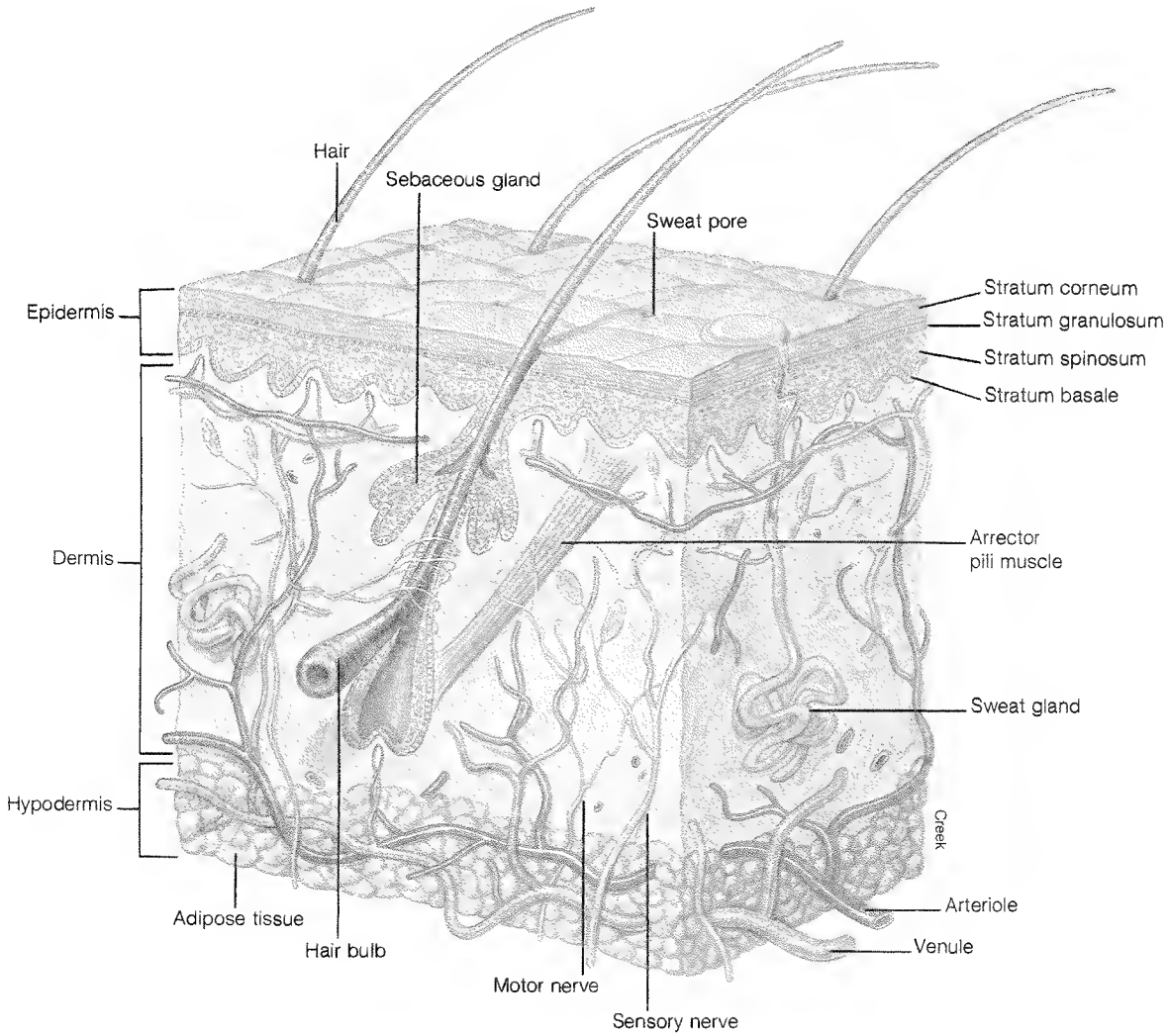

Figure 7.1 A diagram of the skin.